Stochastic Modeling of Tissue Engineering Scaffolds with Varying Porosity Levels

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ABSTRACT

This paper presents a stochastic modeling of tissue engineering scaffolds (porous artifacts) with controlled porosity. The internal architecture of the scaffolds is determined based on a given distribution and porosity level function. The discrete porosity levels are used to determine required expected number of pores for each region of the scaffold. Design variables with random distribution are used to model the spatial location of pores bio-mimetically. Because of the randomness of the distribution of pores, overlapped pores must be determined for calculating the porosity levels accurately. A new computational method based on simulation has been developed to calculate the expected overlapped volumes. Using the calculated overlapping factors, the required numbers of pores are determined to satisfy the required porosity levels at each region. The presented methods are implemented in a computing environment and examples are presented in this paper.

Keywords: tissue scaffolds, heterogeneous porosity, scaffold design, tissue engineering.

1. INTRODUCTION

Tissue engineering is an emerging and interdisciplinary field of biology, biotechnology and biomaterials to replace and restore functions of diseased or damaged tissues [8]. The damaged or diseased tissues are regenerated using complex mold-like structures called tissue scaffolds. Tissue scaffolds are complex structures that help tissue cells to form the final shape of the tissue that meets the replaced tissue's biological and physical requirements. Bio-engineered tissue scaffolds attempts to mimic both the external shape and internal architecture of replaced tissue. The modeling of the scaffolds has a great impact on the growth of the tissue cells and an optimum scaffold design can improve cell growth and proliferation. Tissue scaffolds are usually designed with complex internal architecture that has internal channels and interconnected pores to help cell attachment, cell proliferation, tissue regeneration and nutrient flow. If the regenerated tissue will be used in transplantation, it must meet the shape characteristics of the original tissue. Engineered tissues may also provide some mechanical functions during the regeneration of the replaced tissue. For instance, most bone tissues undergo some mechanical stresses and a bone scaffold must be designed to meet these mechanical loads while the cells are growing inside the scaffolds. Similarly, during regeneration of soft tissues, dynamic loads are applied to scaffolds during healing. In healing process, the shape and the characteristics of the wound are changing which result in dynamic loads to the soft tissue scaffolds. The designed scaffold must withstand the dynamic loads until the complete regeneration of the replaced tissue. Scaffolds also must satisfy some biological requirements such as facilitating cell attachment, helping regeneration and proliferation of tissue cells and transporting of nutrients and signals.

The requirements of the scaffolds can be met by optimizing the internal architecture of the scaffolds. The internal architecture of the scaffolds can be optimized by controlling pore sizes, pore shapes, overall porosity levels and interconnectivity levels of the scaffolds. All these variables have different effects on tissue regeneration and so they must be optimized in modeling of the scaffolds. The degradation rate of a scaffold can be expressed as the scaffold's mass and volume loss with respect to time. After the fabrication of a scaffold, it starts to degrade and finally becomes completely degraded. While the scaffold is degrading, the shapes of the pores and the pH level of the scaffold change and can affect the cell growth. The degradation rate is a key variable to control the environment of a scaffold and it can be controlled by material type, porosity level and pore sizes of the scaffolds.

Since tissue cells attach themselves onto the surfaces of the pores and then those cells starts to grow, the pore sizes and shapes can also affect cell growth. Small pores limit the cell growth and large pores enhance the cell growth. Different pore shapes also affect cell growth, in terms of pore surface area, pore sizes and mechanical characteristics of the scaffolds. Furthermore, pore sizes affect degradation as larger pores cause faster degradation rate.

Total pore volume proportion to scaffold material determines the overall porosity of a scaffold. Higher porosity levels provide enhanced cell growth and cell proliferation, increased degradation rate and lower mechanical characteristics. On the other hand, lower porosity levels provide lower cell growth, lower degradation rate and enhanced mechanical characteristics. If two pores are interconnected, they allow cell and nutrient flow between them. To be able to provide interconnectivity between pores, the pores must be connected or overlapped. Overlapping pores guarantees higher interconnectivity between porous structures. Higher interconnectivity levels help to enhance cell growth and nutrient flow inside the scaffolds. It is very important to optimize those variables for a better tissue scaffold design and hence better tissue regeneration.

Traditionally, the scaffolds are designed with constant porosity levels or homogeneous porosity throughout the scaffolds. In most tissue scaffold design, because of the manufacturing and design limitations, homogeneous porosity levels are commonly used. However, the porosity levels must be optimized at the different regions of the scaffold because of the differences of the spatial biological and mechanical requirements of a replacement tissue. For instance, in one part of a scaffold, high mechanical characteristics might be required while in another part of the scaffold, enhanced cell growth maybe required in a different region. High mechanical characteristics can only be achieved by low level of porosity while enhanced cell growth can be achieved by high level of porosity. In homogeneous design the entire scaffold has a single porosity level and the porosity level is assigned using the worst case scenario. If the porosity level for the better mechanical properties is used to design the scaffold, the cells that require high level of porosity may not grow efficiently.

In this paper, scaffold modeling methodologies with spatially variable porosity levels are proposed. In the heterogeneous design [9], the porosity levels are controlled and optimized spatially so, the local requirements can be met. Instead of assigning one porosity level to the entire scaffolds, different porosity levels is assigned to the different regions of the scaffolds based on the local requirements of the tissue scaffold in heterogeneous porosity design. For instance, bone tissues require higher strength (low porosity), and also they require high level of porosity to enhance cell growth and regeneration. Increasing mechanical properties means decreasing porosity levels and if homogeneous design is used, the entire scaffold will be designed according to the lowest porosity level to meet the mechanical requirements and this can limit the design of the scaffold and cell growth. As shown in the Fig. 1, the engineered tissue scaffold can be designed by controlling the porosity levels spatially to provide required local properties. As mentioned previously, the porosity levels also affect the degradation rate of the scaffolds and regions with higher porosity levels degrade faster due to high degradation surface area and low volume of material. During cell proliferation and growth, cells growth rate must be constant so the degradation rate of a scaffold must be homogeneous. To satisfy the homogeneous degradation rates throughout a scaffold, the regions that contacts with biological fluids and cells must have lower porosity levels than the rest of the scaffolds as shown in Fig. 2. This requirement of the scaffolds also can only be achieved by varying the porosity levels based on the local biological requirements.

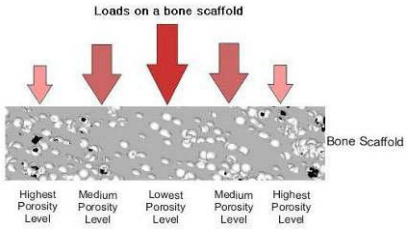


Fig. 1: Example bone scaffold with applied loads.

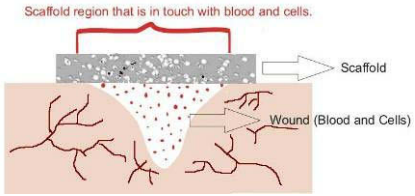


Fig. 2: Wound scaffold example.

This paper proposes a new method for modeling tissue scaffolds with heterogeneous porosity levels. In this modeling method, a scaffold with different porosity levels is developed. As the first step, different porosity regions are defined

and for the required porosity levels, required pore sizes and required numbers of pores are calculated. Finally, these pore sizes and numbers are used to get the three dimensional design of a scaffold.

2. LITERATURE REVIEW

In the literature, the designed tissue scaffolds dictate the bulk form of regenerated tissue shapes, temporarily fulfill the physical function (mechanical, chemical and electrical) of the native tissue and enhance tissue regeneration, vascularization and nutrient flow [2].

Lin et al. and Hollister et al. [6][4]researched the mechanical properties of the degradable scaffolds and their effects. Lin et al. [6] investigated the effects of the porosity level over stiffness. In this research, the optimal level of the porosity is calculated to meet the mechanical requirements of bones. While designing the scaffolds, the required porosity levels and required pore sizes must be calculated in a correct and efficient way. Hollister et al. [4] worked on the optimal design of the bone scaffold. Some example scaffolds and their stiffness results are explained in the paper. They use the homogenization theory to calculate the effective scaffold and regenerated tissue stiffness.

There are several overall design and modeling methodologies for tissue engineering scaffolds. Sun et al. [14] have reviewed several methods in computer-aided design of tissue engineering scaffolds. They also presented the applications of computer-aided design methodologies in tissue engineering in [13]. Das et al. [12][1] have described Image Based Design method (IBD) method using CT scan and the unit library approach to create porous structures bio-mimetically. Similar Image Based Design method approach is also researched by Hollister et al. [3] and Meyer et al. [7]. Hollister et al. [3]created the internal architecture by altering the density in the voxel dataset. Meyer et al. [7]described the biological aspects of the image based approach. The research explained the details of the cell the growth and implantation of the scaffold that is created by the IBD approach to fix the mandibular bone defects.

Several researches developed methodologies to control the internal architecture of scaffold objects to achieve better biological and mechanical properties. Schroeder et al. [11] developed methodologies to model the scaffolds with controlled porosity. The main focus of the paper is finding the distribution of the pores inside the scaffolds to use in the design of the tissue scaffolds. In the paper, after getting the probability distributions of the pores, this distribution is used in scaffold design process. Takano et al. [16] had conducted a research on the characteristics of the micro porous aluminum scaffolds. In this paper, aluminum plates with porosity levels are analyzed to get the design and mechanical characteristics information of the aluminum plate. These heterogeneity methods use the voxel meshing approach for the design and analysis of the porous materials. Karageorgiou et al. [5] conducted a comprehensive research on the relationship between porosity levels and pore sizes of biomaterials used for the bone generation. As explained before, higher porosity and pore size result in greater bone ingrowths; however, increasing porosity levels has a great negative effect on the mechanical properties of the scaffolds. Pores and porosity levels also affect the degradation of the scaffolds and while designing heterogeneous scaffolds. Zang et al. [17] compared different shapes of the pores for the best mechanical characteristics and best cell growth. In this research, spherical pores provided better mechanical characteristics, better cell growth and higher surface area for cell attachment. Sung et al. [15] focused on the effects of the different biomaterials on cell growth and explained the relationship between porosity levels and degradation. They found that higher porosity levels degrade faster than lower porosity levels because higher porosity levels have low amount of material and higher degradation surface area. Santerra et al. [10] summarized the characterization of the scaffold during degradation process. They expressed that higher porosity level causes faster degradation, which causes faster decrease in the mechanical properties of the scaffolds.

To model the scaffolds with varying porosity levels, the required pore sizes, shapes and number of pores need to be calculated. In the following sections the details of the proposed methodology are presented.

3. MODELING TISSUE ENGINEERING SCFFOLDS WITH HETEREGENOUS POROSITY LEVELS

In this research, spheres are chosen as the shape of the pores in the design of the internal structure of scaffolds with heterogeneous porosity regions because they provide better tissue regeneration characteristics [17]. Scaffolds are designed with heterogeneous porosity regions by placing pores inside a scaffold in line with the requirements of scaffolds. Then these spheres are subtracted from the scaffold to create porous structures inside the scaffold. To model the scaffolds bio-mimetically, a stochastic modeling methods is used to determine the location and size of the pores randomly inside the scaffold. In every porosity region, to satisfy the uniform porosity, spheres are located as uniformly

distributed. To provide better interconnectivity between pores, overlapping of pores are allowed while placing the pores randomly inside the scaffold. Therefore spheres/pores are assumed to be non rigid.
To find the actual pore volume, total overlapping volume must be subtracted from the total spheres volume. Since a random distribution is used to locate the spheres inside a scaffold, the expected overlapping volume is used to calculate the overall porosity level of the scaffold region.
Overlapping provides different pore shapes and different pore surface areas. Moreover, the overlapping can be seen as a guarantee for the interconnectivity which is required for the cell growth and fluid, nutrient transportation. Overlapping can directly affect the porosity levels of the scaffold and so it must be considered in the porosity level calculations. Given two spheres with radiuses r_1 and r_2 the overlapping volume can be represented as:

$$OverlappingVolume = \frac{\pi(r_1 + r_2 + d)^2 (d^2 + 2dr_2 - 3r_2^2 + 2dr_1 + 6r_2 r_1 - 3r_1^2)}{12d} \tag{1}$$

where d is the distance between the centers of the spheres.
If the center locations are same there will be a full sphere overlapping and the overlapping volume equals the smaller sphere's volume. There will be overlapping if the following criteria satisfied:

$$r_1 + r_2 > \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2} = d \tag{2}$$

Where (x_i, y_i, z_i) are the center location of the sphere i (i = 1, 2). Eq. (2) describes that if the distances between any two circles' centers are smaller than the summation of the two radiuses, there will be an overlapping.

Then the expected overlapping volume is calculated. The expected overlapping volume is the expected overlapped sphere volume that is created by the random location of the spheres. To find the expected overlapping volume, the following steps are followed:

1) Find out the spheres' center locations (x_j, y_j, z_j) for (x_i, y_i, z_i) that satisfy the $r_i + r_j > \sqrt{(x_j - x_i)^2 + (y_j - y_i)^2 + (z_j - z_i)^2}$ constraint while ($i < j$).
2) Use the spheres found in step 1, to calculate the overlapping volume by using Eq. (1).
3) Get the probability distribution of the overlapping volume.
4) Find the expected overlapping volume from the distribution.

Expected overlapping volume of n overlapping spheres can be expressed using the following equation:

$$EOV^n = \sum_{Overlapping^n=1}^{TNO^n} V_{Overlapping^n} \cdot p(V_{Overlapping^n}) \tag{3}$$

where EOV^n = Expected n sphere overlapping volume for a single overlapping.
$V_{Overlapping^n}$ = Volume of the n sphere overlapping.
$p(V_{Overlapping^n})$ = Probability of getting $V_{Overlapping^n}$ as n sphere overlapping.
TNO^n = Total number of n sphere overlapping occurred in a scaffold.

After calculating the EOV^n, which is the expected overlapping volume of a single n sphere overlapping, total expected overlapping must be determined. Total expected overlapping volume (TEOV) is the expected total overlapping volume that is occurred in a single scaffold and caused by the all spheres' overlapping inside the final designed scaffolds.
By using these n overlapping calculations, *TEOV* can be found as follows:

$$TEOV = \binom{N}{2} * P_{Overlapping^2} * EOV^2 + \binom{N}{3} * P_{Overlapping^3} * EOV^3 + \ldots + \binom{N}{N} * P_{Overlapping^N} * EOV^N \tag{4}$$

In Eq. (4), $P_{Overlapping^n}$ is the probability of n different spheres overlapping.
By using two spheres overlapping probability the formulation can be generalized for probability of overlapping of n different spheres as:

$$P_{Overlapping_n} = \left(\frac{m}{L}\right)^{\left((n)*(n-1)/2\right)} \tag{5}$$

Where m = Total number of the locations that satisfy a overlapping around a single sphere. L = Overall possible locations for a center of a sphere inside the scaffold. While $n \rightarrow \infty$, the limit of $P_{Overlapping_n}$ will converge to zero. Because m >> L inside scaffolds, that is, spheres are really smaller than the scaffolds and this decreases the probability of overlapping to a small number. Because of the probability converges to zero, some of the overlapping can be neglected:

$$P_{Overlapping^3} * EOV^3 = P_{Overlapping^4} * EOV^4 = ... = P_{Overlapping^N} * EOV^N = 0 \quad (6)$$

If this assumption applied to the *TEOV* formula, the total volume of overlapping can then be expressed as:

$$TEOV = \binom{N}{2} * P_{Overlapping^2} * EOV^2 \quad (7)$$

3.1 Stochastic Design of Internal Architectures of Scaffolds

In this section, stochastic methods is developed to find the overlapping probability and expected overlapping volume of the scaffolds. Overlapping factor (*OF*) is used to calculate the percentage of overlapping between two or more spheres. *OF* can be described as the ratio of the total overlapping volume and the total volume of the spheres.

$$OF = \frac{V_{Overlapping}}{V_{Spheres}} \quad (8)$$

Where $V_{Overlapping}$ = Total overlapping volume inside the scaffold. $V_{spheres}$ = Total volume of the spheres.

Then the porosity level can be calculated as follows:

$$PorosityLevel\% = \left(\frac{V_{Spheres} * OF}{V_{Scaffold}} \right) * 100 \quad (9)$$

Where *Porosity Level* = Proportion of volume of pores inside the scaffold and volume of the scaffold without pores. $V_{Scaffold}$ = Total volume of the scaffold.

To calculate the closed form equations of *OF*, statistical based design methods are used. To get *OF* formulation, the experimental design is developed using the different values of sphere radiuses and number of spheres for the same scaffold design.

In the design process of the scaffold, the radiuses of spheres, porosity levels and the scaffold volume are the inputs of the model and using these variables, the required number of spheres is calculated to satisfy the required porosity levels. *OF* formulation is determined from the design experiments and it is dependent on to the expected values of number of spheres *N* and radius *r* values. The developed stochastic model takes radii, number of spheres, scaffold volume and porosity regions as input for the model and creates the design of the scaffold with regional porosity requirements. The model also calculates the overlapping volume that occurred in each experiment and this overlapping volume information can be used while formulating *OF*. Several experimental runs are generated to determine the distribution of the overlapped volume. For sample runs, the uniformly distributed pores and pores locations in a unit volume are used. The overlapping volume is calculated. The overlapping volume found from the experiments is shown in Fig. 3.

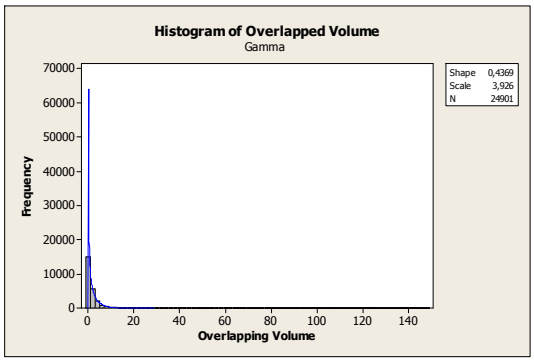


Fig. 3: Histogram of overlapping volume.

Fig. 3 shows the distribution of the overlapping volume. The distribution of the overlapping volume is determined to be a Gamma distribution using statistical analysis. The gamma distribution variables that describe the overlapping volume are found from the histogram of the overlapping volume and then it can be used in the calculation of expected overlapping volumes.

For calculating the overlapping factor formula, the model is run for the different levels of the *N* and *r*. By using the different levels of *N* and *r*, the experimental design is developed for different values of *N* and *r* combination in 5 different designs. From each design, the *OF* values are obtained and then transferred to Minitab® Software for statistical analysis and for finding the formulation for *OF*.

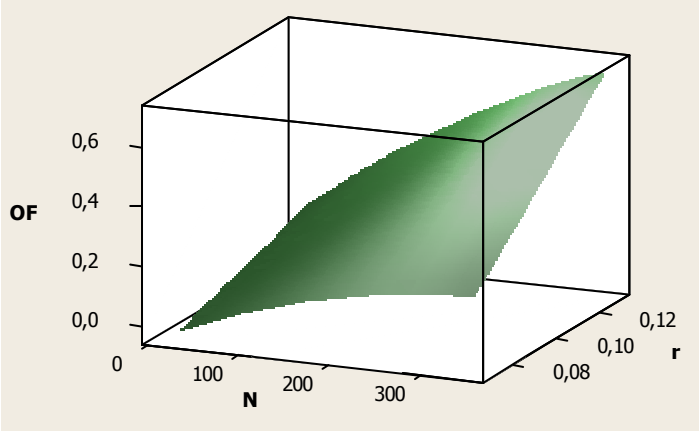


Fig. 4: Response surface for *OF* values.

Fig. 4 describes the *OF* values the different levels of *N* and *r* for the unit scaffold design (1 *mm* Cube). The results of the simulation runs are used to get the formulation of *OF*. To find out the formulation of *OF*, results from each design is statistically analyzed. The result of the analysis can be summarized in a table as follows:

Estimated Regression Coefficients for OF	
Term	Coefficients
Constant	-0,20854
N	0,00026
r	2,08560
N*N	0,00000
r*r	1,54519
N*r	0,01669

Tab. 1: General regression model of *OF* values.

This general regression model describes the *OF* factors as a function of *N* and *r* as follows:

$$OF = -0.20854 + (0.00026 * N) + (2.08560 * r) + (1.54519 * r^2) + (0.001669 * N * r) \quad (10)$$

Using the *OF* equation, the overlapping factor can be calculated and it can be used in the design of the scaffold with heterogeneous porosity levels.

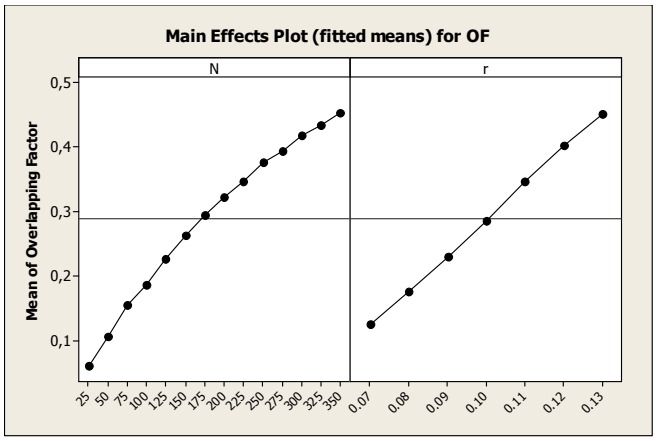


Fig. 5: Main effects plot of *N* and *r*.

In Fig. 5, the main effects of *N* and *r* can be seen. As shown in the figure, if the levels of *N* or *r* increased, the overlapping volume increases.

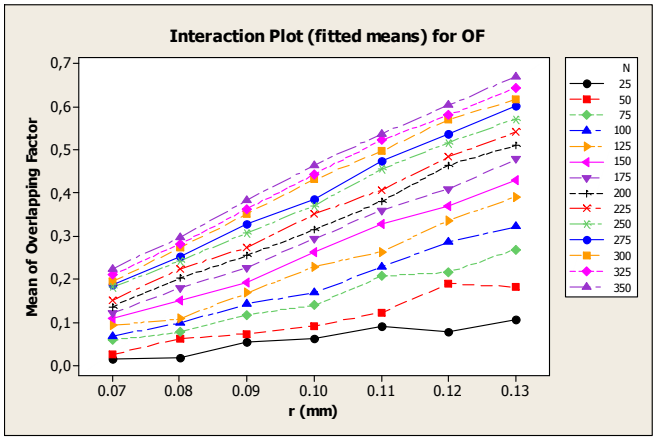


Fig. 6: Interaction effects plot of *N* and *r*.

Fig.6 shows the interaction effect plot for *N* and *r*. Based on the results of the interaction effect plot, it can be observed that between *N* and *r*, there is no serious interaction effect; this means that *N* and *r* affect *OF* independently and do not cause unexpected changes in *OF* values.

The last statistical analysis is residual analysis. Residual is the standard deviation of the *OF* values. By the help of the residual analysis, statistical validity of the *OF* formulation is analyzed. From the residual analysis, residuals are found as normally distributed and independent. Hence, the *OF* model can be used as a statistically qualified model. We can conclude that the formulation of *OF* can be used in the design process of the scaffolds, because the formulation of *OF* statistically represents the real *OF* values.

Number of the spheres for the required porosity levels needs to be calculated. If the *OF* formulation is known, the number of the spheres can be calculated by inserting the regression model of *OF* in Eq. (3), a new porosity level calculation is expressed as:

$$PorosityLevel = \left(\frac{N * \frac{4}{3} * \pi * r^3 * (-0.20854 + 0.00026N + 2.0856r + 1.54519r^2 + 0.001669Nr)}{V_{Material}} \right) \quad (11)$$

After simplifications, N is found as follows:

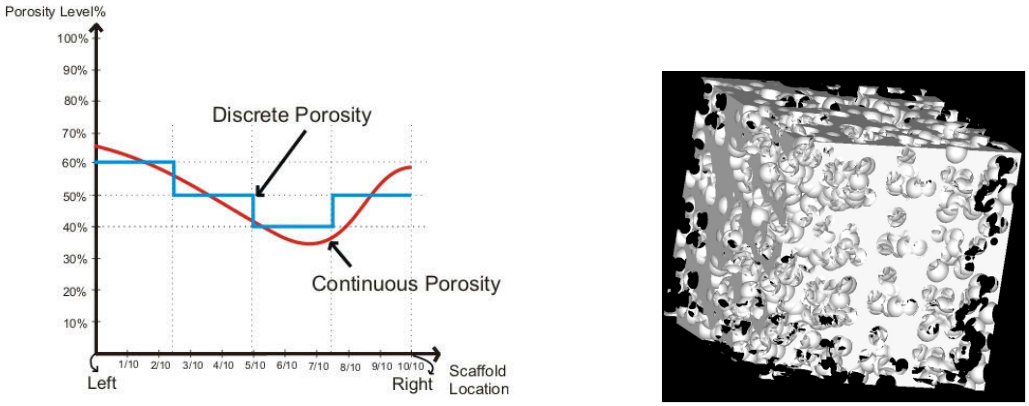
$$N * (-0.87353r^3 + 8.73614r^4 + 6.47248r^5) + N^2 * (0.001089r^3 + 0.006991r^4) = PorosityLevel * V_{Material} \quad (12)$$

The roots of the equation will give the required number of spheres for the required porosity level.

4. IMPLEMENTATION AND EXAMPLES

While designing the scaffolds, important criteria are final scaffold shape and the porosity regions. After obtaining these variables, the presented heterogeneous scaffold design methodology can be used to get a heterogeneous scaffold designs. In this chapter, the heterogeneous designed scaffolds, their porosity distributions and their 3D design will be presented.

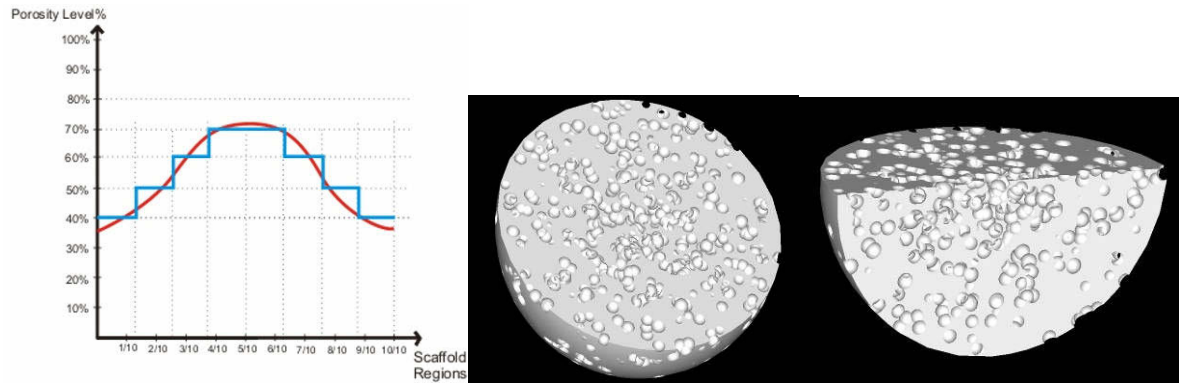
In the first example, 2 *mm* cube is used as main scaffold geometry. The pores are chosen to be 300 μ. Fig. 7 shows the required porosity levels throughout the scaffold. However in the design method, discrete porosity regions are used as shown Fig. 7. After determining the porosity regions, the external scaffold design and porosity regions are combined together. Fig. 7 (b) shows the final 3D scaffold design. Porosity of the scaffold follows the discrete porosity function in Fig. 7. i.e. the left and right sides of the object are more porous.



(a) (b)

Fig. 7: (a) Required porosity distribution plot and discrete porosity regions, (b) Final design for block example with pores.

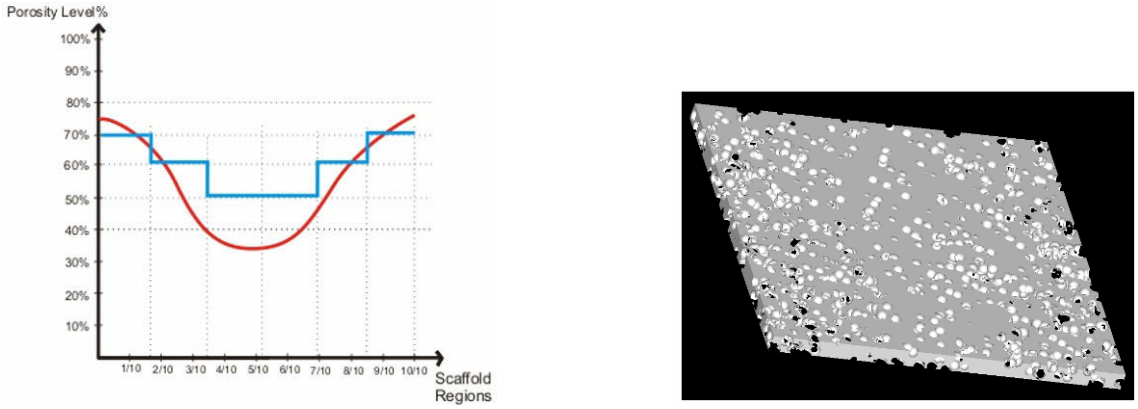
A spherical geometry is chosen for second example. The porosity distribution function is implemented in the design of the scaffold in Fig. 8(a). Using the required porosity levels, the regions are divided to discrete regions of spheres. After calculating the porosity levels for each region, the final 3D scaffold design is shown in Fig. 8(b). As shown in the figure, the center of the sphere is more porous and the porosity is decreasing from center to the outer surface. By controlling the porosity throughout the scaffold, the interconnectivity of the pores is also controlled. As shown in the figure, the center section of the scaffold object is more porous or highly interconnected which helps nutrient flow inside the scaffolds and provides better biological properties. While, the areas closer to the outer surface is less-interconnected and might block the nutritional flow but it provides better mechanical properties. Therefore, it is very important to optimize the porosity distribution function given in Fig. 8(a) for a better tissue scaffold design and hence better tissue regeneration.



(a) (b)

Fig. 8: (a) Porosity distribution plot and discrete porosity regions, (b) Final design of spherical scaffold with pores.

As a skin scaffold example, a heterogeneous thin block scaffold is used. The block sizes are 6 *mm* x 6 *mm* x 0.3 *mm*. Pore radii are uniformly distributed between 90 μ and 100 μ. The required porosity level is in Fig. 9(a). This required porosity distribution must be used in the heterogeneous scaffold design and to use in the method it has to be divided into discrete regions. The final 3D design of the example scaffold is shown in Figure 9(b). As shown in the figure, the left and right sides of the scaffold are more porous than the center region of the scaffold.



(a) (b)

Fig. 9: (a) Porosity distribution plot and discrete porosity regions, (b) Final skin scaffold design.

5. CONCLUSIONS

The new stochastic design methodology developed to model tissue engineering scaffolds with heterogeneous porosity levels in this paper. The developed methodologies calculate the required number of pores to satisfy the required porosity levels at different regions of the scaffold using the statistically calculated overlapping factor. Three dimensional scaffolds with heterogeneous porosity regions design procedures were developed to create a three dimensional scaffold design. Finally, the proposed method is used to obtain the example three dimensional scaffold designs with heterogeneous porosity regions. Using the developed methods, tissue scaffolds can be designed to provide different properties at their different regions. Using heterogeneous porosity levels can greatly provide the required biological and mechanical properties of the regenerated tissues.

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